Original Article

http://dx.doi.org/10.3349/ymj.2013.54.2.283
pISSN: 0513-5796, eISSN: 1976-2437

Yonsei Med J 54(2):283-287, 2013

YMJ

Metabolic Syndrome with Hyperglycemia and the Risk of Ischemic Stroke

Mengnan Li, Yan Li, and Junyan Liu

Department of Neurology, The Third Hospital of HeBei Medical University, Shijiazhuang, China.

Received: March 15, 2012
Revised: June 8, 2012
Accepted: June 13, 2012
Corresponding author: Dr. Junyan Liu,
Department of Neurology,
The Third Hospital of HeBei Medical University,
The 139th of Zi Qiang Road,
Shijiazhuang 050051, China.
Tel: 13313012890, Fax: 86-0311-87023626
E-mail: junyanliu2003@yahoo.com.cn

· The authors have no financial conflicts of interest.

Purpose: The association of ischemic stroke and metabolic syndrome (MetSyn) with or without diabetes mellitus (DM) is not clear. The present study aimed to identify the impact of diabetes or hyperglycemia on the risk of MetSyn-associated ischemic stroke. **Materials and Methods:** This study comprised an Asian population of 576 patients with acute nonembolic cerebral infarction and 500 controls. MetSyn was defined according to the criteria of the International Diabetes Federation. MetSyn patients were further subgrouped according to their glucose levels: MetSyn with DM, MetSyn with impaired fasting glucose (IFG) and MetSyn with normal glucose tolerance (NGT). The impact of MetSyn on cerebral infarction was then evaluated. **Results:** At baseline, the prevalence of MetSyn in patients with cerebral infarction was higher than that of the controls (57.29% vs. 10.00%, $p<0.01$). In the stroke group, the prevalences of MetSyn with DM, IFG, and NGT were 25.69%, 8.85% and 22.74%, respectively, all of which were higher than that of the controls (all p-values <0.05). By multiple logistic regression analysis, we discovered that MetSyn was associated with an increased risk of cerebral infarction (odds ratio: 5.73, $p<0.01$). After adjustment for all the components of MetSyn, the odds ratios of MetSyn with DM, IFG, and NGT were 5.70, 2.24 and 2.19 (all p-values <0.05), respectively. **Conclusion:** In Asian population, patients with MetSyn accompanied by T2DM are at the greatest risk for acute non-embolic stroke. Additionally, IFG was not observed to be associated with an increased risk for MetSyn-related ischemic stroke.

Key Words: Metabolic syndrome, cerebral infarction, hyperglycemia, diabetes

INTRODUCTION

Metabolic syndrome (MetSyn) is a constellation of inter-related metabolic abnormalities that include insulin resistance, diabetes, elevated blood pressure, obesity, and dyslipidemia. MetSyn is recognized to increase the risk of cardiovascular disease, cardiovascular morbidity and mortality.[1-4] Several epidemiologic studies have indicated that MetSyn involves an increased risk of ischemic stroke.[3,5-10]

As defined by the National Cholesterol Education Program and the Third Adult Treatment Panel,[11] many of the features of MetSyn such as impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) can be used as predictors of diabetes.

Thus, MetSyn may indicate a prediabetic state.[12-14] Nevertheless, there is controversial evidence regarding the incremental vascular risk associated with MetSyn without diabetes mellitus (DM). A recent study[8] of T2DM subjects with MetSyn indicated that T2DM did not increase the risk of ischemic stroke. In the present population-based case-control study, we evaluated MetSyn with and without DM or IFG as risk factors of acute ischemic/nonembolic stroke.

MATERIALS AND METHODS

Subjects

A total of 576 patients (346 men, 230 women) who were hospitalized for acute ischemic stroke (within 2 weeks from symptom onset) from June 2004 to January 2007 at the Third Hospital of Hebei Medical University were included as the stroke group. Additionally, 500 volunteers (301 men, 199 women), who were consecutively evaluated as part of the medical examinations, were included as the control group. This study received ethical approval from the Third Hospital of Hebei Medical University, and informed consent was obtained from all subjects before enrollment in the study.

Subjects in the control group were matched with the stroke group for both age and sex (Table 1). Among these, subjects with a history of stroke were excluded. Criteria for inclusion in the study were as follows: 1) patients who visited the Department of Neurology at the Third Hospital of Hebei Medical University within 12 h of the onset of symptoms; 2) the diagnosis of acute ischemic/nonembolic stroke was based on history (clinical course, associated symptoms such as facial paralysis, slurred speech, dysarthria, and hemiparesis), physical examinations (including neurologic and cardiac assessments), and radiologic study (initial noncontrast brain CT scan or MRI). Further confirmation included full cardiac evaluation (history and physical electrocardiograms) and transcranial Doppler ultrasound to exclude a cardiac or carotid artery source of embolism. Subjects with a history of active infections, neoplasia, renal or liver diseases, and thyroid dysfunction were excluded.

Vascular risk factors

Body weight, height, waist circumference, and blood pressure were measured. Body mass index was calculated as the weight of the subjects in kilograms divided by the square of their height in meters.[15] After fasting for 8 hours, blood samples were taken to assess plasma glucose, total cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) levels. In addition, subjects were administered an oral glucose tolerance test (OGTT) once their fasting plasma glucose level reached ≥5.6 mmol/L. Cigarette smoking status data were collected in a structured interview. All laboratory and clinical investigations were evaluated 4 weeks after the onset of acute ischemic stroke.

Definition of IFG and T2DM

Normal fasting glucose, IFG, and T2DM were defined according to the criteria of the American Diabetes Association.[16] Normal glucose tolerance (NGT) was defined as a fasting plasma glucose level of <5.6 mmol/L or a 2-h OGTT glucose of <7.8 mmol/L. IFG was considered for a fasting plasma glucose level of 5.6-6.9 mmol/L.[17] We defined IGT

Table 1. Clinical and Laboratory Characteristics of the Study Population

Clinical characteristics	Ischemic stroke (n=576)	Control (n=500)	*p* value
Sex, male (%)	346 (60.06)	301 (60.20)	0.98
Age mean age±SD	63.00±11.78	62.78±8.46	0.894
Smoking history, n (%)	289 (50.17)	122 (24.40)	0.001
Waist, cm			
Male	97.08±10.10	96.88±11.11	0.964
Female	86.18±9.71	84.85±11.96	0.962
Central obesity	355 (61.63)	280 (56.00)	0.141
Hypertension, n (%)	431 (74.83)	186 (37.20)	0.001
TG, mmol/L	1.81±1.12	1.70±1.01	0.709
HDL-C, mmol/L	1.22±0.35	1.43±0.38	0.045
TC, mmol/L	5.28±1.21	5.21±1.44	0.942
LDL-C, mmol/L	3.23±0.98	3.23±0.92	0.975
FBG, mmol/L	6.24±1.55	5.40±0.94	0.038

HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; TG, triglyceride; TC, serum total cholesterol; LDL-C, low density lipoprotein cholesterol; FBG, fasting blood glucose.

as a 2-h OGTT glucose level of 7.8-11.0 mmol/L. T2DM was defined as a fasting plasma glucose level of ≥7.0 mmol/L, a 2-h OGTT glucose of ≥11.1 mmol/L, or the use of hypoglycemic drug therapy.

Definition of metabolic syndrome (MetSyn)

According to the International Diabetes Federation definition,[16] participants were defined as having MetSyn if he or she demonstrated central obesity (a waist circumference of ≥90 cm in men or ≥80 cm in women based on the Asia-Pacific consensus[15]) plus two or more of the following criteria: 1) a triglyceride level of ≥1.69 mmol/L (150 mg/dL); 2) a HDL-C level of <1.04 mmol/L (40 mg/dL) in men and <1.29 mmol/L (50 mg/dL) in women; 3) systolic or diastolic blood pressure of ≥130/85 mm Hg or previously diagnosed hypertension; and 4) a fasting plasma glucose level of ≥5.6 mmol/L (100 mg/dL) or a previous diagnosis of T2DM.

Statistical analyses

First, the chi-square (χ^2) test was used to evaluate differences in baseline characteristics among MetSyn and different glucose status categories. Then multiple logistic regression models were employed to determine the multivariate associations of MetSyn after adjusting for cofounders, components and other vascular disease risk factors. All odds ratios (ORs) were calculated for all subjects with MetSyn accompanied by DM, IFG, or NGT. The component conditions of MetSyn were included as categorical variables. All analyses were carried out with Statistical Package for the Social Sciences (SPSS) 11.0 software (Beijing Hope Electronic Press, Beijing, China). All reported *p*-values are two-tailed, and *p*-values of <0.05 were considered statistically significant.

RESULTS

Prevalence of MetSyn according to glucose status (DM, IFG, and NGT)

MetSyn was more frequent among patients with acute ischemic/nonembolic stroke compared to those in the control group (57.29% vs. 10.00%, χ^2=262.048, p<0.01). Compared to the controls, participants with stroke exhibited a higher prevalence of MetSyn with DM (25.69% vs. 3.20%, p<0.001), IFG (8.85% vs. 2.20%, p<0.001), and NGT (22.74% vs. 4.60%, p<0.001) (Table 2).

Prevalence of DM, IFG, NGT according to oral glucose tolerance test (OGTT)

There were 363 participants who demonstrated a fasting glucose level of ≥5.6 mmol/L in the stroke group. According to OGTT, 87 participants were diagnosed as diabetic, 72 participants had IFG, 106 participants were IGT, 17 participants were both IFG and IGT, and 81 participants were NGT. In other words, according to OGTT, the detected prevalences of DM, IFG and IGT were 23.97%, 24.52% and 33.88%, respectively, in the stroke group. In contrast, in the control group, 74 participants were administered the OGTT, and among them, 16 participants had DM, 14 participants had IFG, and 22 participants were IGT. The prevalence of DM was 21.62%.

Ischemic stroke is associated with MetSyn in subjects of different glucose status

On multiple logistic regression analysis, after adjustment for age, gender and smoking habits, the ORs for ischemic stroke were 11.24 (95% CI: 6.49-19.48, p<0.001) in subjects with MetSyn and DM; 4.60 (95% CI: 2.43-8.68, p<0.00) in subjects with MetSyn and IFG; and 4.15 (95% CI: 2.45-7.05, p<0.001) in subjects with MetSyn and NGT. When further adjusted for other known components of MetSyn, such as hypertension, high serum LDL-C and central obesity, the risk remained, and the ORs of ischemic stroke were 5.70, 2.24, and 2.19 in subjects with MetSyn and DM, IFG, or NGT, respectively (p<0.05) (Table 3).

DISCUSSION

The present results suggest that MetSyn is a strong independent risk factor for acute ischemic/nonembolic stroke.

Table 2. Prevalence of MetSyn According to Glucose Status

Prevalence	Ischemic stroke	Control	X^2	*p* value
MetSyn	57.29% (330/576)	10.00% (50/500)	62.048	<0.01
MetSyn with DM	25.69% (148/576)	3.20% (16/500)	104.837	<0.001
MetSyn with IFG	8.85% (51/576)	2.20% (11/500)	21.825	<0.001
MetSyn with NGT	22.74% (131/576)	4.60% (23/500)	71.841	<0.001

DM, diabetes mellitus; IFG, impaired fasting glucose; NGT, normal glucose tolerance; MetSyn, metabolic syndrome.

Table 3. MetSyn-Associated Ischemic Stroke in Subjects of Different Glucose Status

Risk factor	Chi-square	OR	95% CI	*p* value
Smoking history	75.317	7.34	6.91-14.05	<0.001
MS with DM	20.922	5.70	3.16-10.28	<0.001
MS with IFG	10.362	2.24	1.11-4.51	<0.001
MS with NGT	7.167	2.19	1.25-3.86	0.018
Sex	0.136	2.02	1.15-3.69	0.545
Age	-	1.78	0.99-3.02	0.636

OR, odds ratio; MetSyn, metabolic syndrome; DM, diabetes mellitus; IFG, impaired fasting glucose; NGT, normal glucose tolerance.

This association was not attenuated after adjustment for the presence of established cardiovascular and cerebrovascular risk factors, such as age, gender, current smoking, DM or hypertension. The prevalence of MetSyn was significantly higher among subjects with ischemic stroke compared to the controls (57.29% vs.10.00%, $p<0.05$), independent of other confounding factors such as age, gender and smoking. The OR for ischemic stroke was 11.24 (95% CI: 6.49-19.48, $p<0.001$) in subjects with both MetSyn and DM, while after further adjustment for other known MetSyn components, such as hypertension, high serum LDL-C and central obesity, the OR for ischemic stroke was 5.70 in subjects with both MetSyn and DM. These results are in agreement with recent studies[18-20] that showed that MetSyn is associated with an increased risk of ischemic stroke morbidity and mortality, with risk estimates ranging from 2- to 14.7-fold.

According to the multiple logistic regression analyses performed in this study, MetSyn with or without DM was found to be associated with an increased risk of ischemic stroke. The risk of ischemic stroke in subjects with both MetSyn and DM was higher compared to subjects with MetSyn only but no DM, indicating that MetSyn could be used as a risk factor of ischemic stroke, even in the absence of DM. It should be noted that there is controversial evidence regarding the incremental vascular risk associated with MetSyn in non-DM subjects, as recent data from a study of T2DM subjects with MetSyn showed that ischemic stroke risk did not increase as a function of MetSyn.[8] Differences between the results of that study and ours may be due to the differences in the ethnicities of the subjects (Greek patients with a Mediterranean diet vs. Asians). In addition, the mean age of the diabetic population in their study was lower than that of our study subjects (stroke group 64.8±7.2 vs. 63.00±11.78, controls 59.7±9 vs. 62.78±8.46, respectively).

According to the Framingham Offspring Study,[21] MetSyn is almost three times as prevalent as diabetes, imposes greater adverse impact and accounts for more strokes than overt diabetes. In other words, the incidence of atherosclerotic cardiovascular disease and stroke is more attributable to MetSyn than to diabetes. However, the Northern Manhattan Study,[22] a multiethnic, prospective, population-based cohort study of nondiabetic individuals, showed that insulin resistance estimated by a homeostasis model assessment in the fourth quartile (vs. quartiles 1-3) is associated with a 2.8-fold increased risk of first ischemic stroke. After adjustment for established cardiovascular risk factors, including glucose level and obesity, MetSyn did not attenuate the association with ischemic stroke. Therefore, further studies are needed to clarify whether MetSyn is associated with ischemic stroke in DM and non-DM individuals.

In the present study, MetSyn-associated ischemic stroke was similar in groups with IFG or NGT (with ORs of 2.24 and 2.19, respectively). This is in agreement with recent studies, in which IFG was not associated with an increased risk of ischemic stroke,[23] while IGT (a glucose level of 140-199 mg/dL 2 h after a glucose load) was significantly associated with ischemic stroke.[24] In addition, we found that 23.97% of subjects with DM in the present study were not diagnosed by the measurement of fasting glucose alone. These are important findings, because the standard definition of MetSyn is a fasting glucose of ≥5.6 mmol/L or previously diagnosed T2DM, rather than by results of IGT or OGTT.[16] While the measurement of fasting glucose during an acute episode of stroke may be considered a limitation of the study, many subjects with normal fasting glucose levels exhibit insulin resistance. In addition to the role of glucose status (NGT, IFG, or DM), there are other aspects of glucose metabolism that may act as risk factors for ischemic stroke, especially hyperinsulinemia and increased insulin resistance. We, therefore, suggest that clinicians pay more attention to OGTT and IGT in the definition and assessment of MetSyn.

In summary, our results suggest that MetSyn is associated with an increased risk of acute non-embolic stroke in Asian populations, especially in patients with DM or hyperglycemia. Our findings provide important information to-

ward better characterization of individuals who are at increased risk of stroke.

ACKNOWLEDGEMENTS

We would like to thank Medjaden Bioscience Limited for assisting in the preparation of this manuscript.

REFERENCES

1. Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K; DECODE Study Group. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. Arch Intern Med 2004;164:1066-76.
2. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care 2005;28:385-90.
3. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 2003;107:391-7.
4. Katzmarzyk PT, Church TS, Blair SN. Cardiorespiratory fitness attenuates the effects of the metabolic syndrome on all-cause and cardiovascular disease mortality in men. Arch Intern Med 2004;164:1092-7.
5. Chen HJ, Bai CH, Yeh WT, Chiu HC, Pan WH. Influence of metabolic syndrome and general obesity on the risk of ischemic stroke. Stroke 2006;37:1060-4.
6. Iso H, Sato S, Kitamura A, Imano H, Kiyama M, Yamagishi K, et al. Metabolic syndrome and the risk of ischemic heart disease and stroke among Japanese men and women. Stroke 2007;38:1744-51.
7. Ninomiya T, Kubo M, Doi Y, Yonemoto K, Tanizaki Y, Rahman M, et al. Impact of metabolic syndrome on the development of cardiovascular disease in a general Japanese population: the Hisayama study. Stroke 2007;38:2063-9.
8. Bruno G, Merletti F, Biggeri A, Bargero G, Ferrero S, Runzo C, et al. Metabolic syndrome as a predictor of all-cause and cardiovascular mortality in type 2 diabetes: the Casale Monferrato Study. Diabetes Care 2004;27:2689-94.
9. Stern MP, Williams K, Hunt KJ. Impact of diabetes/metabolic syndrome in patients with established cardiovascular disease. Atheroscler Suppl 2005;6:3-6.
10. Ovbiagele B, Saver JL, Lynn MJ, Chimowitz M; WASID Study Group. Impact of metabolic syndrome on prognosis of symptomatic intracranial atherostenosis. Neurology 2006;66:1344-9.
11. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
12. Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2008. [accessed on 2010 December 25]. Available at: http://www.diabetes.org/diabetes-basics/diabetes-statistics/?utm_source=WWW &utm_medium=DropDownDB&utm_content=Statistics&utm_campaign=CON.
13. Haffner SM. Insulin resistance, inflammation, and the prediabetic state. Am J Cardiol 2003;92:18J-26J.
14. Hsueh WA. Introduction: new insight into understanding the relation of type 2 diabetes mellitus, insulin resistance, and cardiovascular disease. Am J Cardiol 2003;92:1J-2J.
15. Western Pacific Regional Office of the World Health Organization. The International Obesity Task Force. The Asia-Pacific perspective: redefining obesity and its treatment. Sydney: Health Communications Australia; 2000.
16. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183-97.
17. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006;23:469-80.
18. Milionis HJ, Rizos E, Goudevenos J, Seferiadis K, Mikhailidis DP, Elisaf MS. Components of the metabolic syndrome and risk for first-ever acute ischemic nonembolic stroke in elderly subjects. Stroke 2005;36:1372-6.
19. Gorter PM, Olijhoek JK, van der Graaf Y, Algra A, Rabelink TJ, Visseren FL; SMART Study Group. Prevalence of the metabolic syndrome in patients with coronary heart disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm. Atherosclerosis 2004;173:363-9.
20. Bang OY, Kim JW, Lee JH, Lee MA, Lee PH, Joo IS, et al. Association of the metabolic syndrome with intracranial atherosclerotic stroke. Neurology 2005;65:296-8.
21. Najarian RM, Sullivan LM, Kannel WB, Wilson PW, D'Agostino RB, Wolf PA. Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke: the Framingham Offspring Study. Arch Intern Med 2006;166:106-11.
22. Rundek T, Gardener H, Xu Q, Goldberg RB, Wright CB, Boden-Albala B, et al. Insulin resistance and risk of ischemic stroke among nondiabetic individuals from the northern Manhattan study. Arch Neurol 2010;67:1195-200.
23. Noto D, Barbagallo CM, Cefalù AB, Falletta A, Sapienza M, Cavera G, et al. The metabolic syndrome predicts cardiovascular events in subjects with normal fasting glucose: results of a 15 years follow-up in a Mediterranean population. Atherosclerosis 2008;197:147-53.
24. Urabe T, Watada H, Okuma Y, Tanaka R, Ueno Y, Miyamoto N, et al. Prevalence of abnormal glucose metabolism and insulin resistance among subtypes of ischemic stroke in Japanese patients. Stroke 2009;40:1289-95.